Memorandum to File
Pharmacology/Toxicology, Division of Nonprescription Drug Products
Reviewer: D. Charles Thompson, RPh, PhD, DABT

TSI: 1355	Sponsor: Multiple
Drug: Acetaminophen (APAP)	Indication: Pain, fever

Subject: TSI 1355: Review #2 of Nonclinical Published Literature

Background

A new Track Safety Issue (TSI-1355) was opened on 1 April 2014 following a report by Cooper et al. (JAMA Pediatr. 168(4):306-7, 2014) suggesting a possible link between APAP use in pregnant women and the development of attention-deficit/hyperactivity disorder (ADHD) in their offspring. Please refer to the previous memorandum on this topic for additional background information (Nonclinical Review, D.C. Thompson, 8 February 2016). The current memorandum provides an update on relevant activity since the previous memorandum as well as a review of the more recent nonclinical literature.

Activity since February 2016

A second review of the published clinical literature was filed by CDER/OSE on 14 October 2016, prompted by DNDP consultation for review of recently published epidemiological studies (TSI-1355: Epidemiology: Review of published study, A.D. Mosholder, 16 October 2016). This review concludes that there is "…growing evidence for adverse neurodevelopmental outcomes being associated with in utero APAP exposure, even in the absence of proof of a causal relationship" and that "…it would be appropriate for FDA to bring this issue to the attention of consumers and health care providers through one of the communication avenues available to the agency." Importantly, CDER/OSE further concludes that, "With respect to further evaluation of this signal, it may be beneficial to re-consult Pharmacology/Toxicology to ask whether any preclinical models might address any of the expanded spectrum of neurodevelopmental outcomes that have now been associated with prenatal APAP exposure."

Pursuant to this CDER/OSE review, general consults were issued to DBRUP and DPMH and a TSI-1355 team meeting was held on 6 February 2017 to discuss conclusions and recommended next steps. Final Consult Reviews are now available in DARRTS from DBRUP (TSI-155: Memorandum of Consultation, C.P. Nguyen, 10 February 2017) and DPMH (TSI-1355: Maternal Health Memorandum, T.N. Johnson, 17 April 2017).

Review and Evaluation of More Recent Nonclinical Published Literature

Following a meeting for TSI-1355 on 24 April 2017, the nonclinical review teams from DNDP and DAAAP worked to assess the relevant data gaps for APAP and options for nonclinical testing to address the concerns raised by OSE reviewer, Dr. Mosholder. The review focused on literature published since the previous nonclinical review was drafted for TSI-1355. The relevant references are listed in the table appended at the end of this document (**Appendix 1**). In addition, DAAAP has recently reviewed the published

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literature for relevant nonclinical data as part of a PLLR labeling conversion supplement for NDA 022450 (Ofirmev® (acetaminophen for injection), Mallinckrodt Inc.) (NDA 022450: Pharmacology/Toxicology Review, C.K. Huynh, 10 January 2017). These data, plus the clinical literature as reviewed by Dr. Mosholder, were summarized and discussed at a meeting of the Neurotoxicity Assessment Subcommittee (NAS) of the CDER/OND Pharmacology/ Toxicology Coordinating Committee (PTCC) on 12 October 2017. A summary of discussion and conclusions from this meeting are provided below.

Summary of NAS Meeting, 12 October 2017

- Exact mechanism of action of APAP is not clear. But there is evidence for CNS acting effects.
- Since DSC issued on 9 January 2015, more clinical publications followed suggesting slight increased hazard ratio for behavioral effects such as ADHD, motor effects, hyperkinetic syndrome, etc. with use of APAP in pregnancy.
- DEPI would like to update the DSC to discuss evidence for potential neurodevelopmental harm to the fetus from maternal APAP use. The epidemiology data are confounded and not conclusive.
- Question from DEPI: Are there nonclinical studies that could be conducted to add to the understanding of a potential linkage between maternal APAP use and neurodevelopmental deficits in children?
- Concerns:
    - Clinical signal is very small for APAP-ADHD relationship: Hazard ratio of ~1.2–1.4 for maternal APAP use and observation of ADHD.
    - There are no established ways to evaluate ADHD-like behavioral endpoints in animals.
    - Limited understanding of histopathological correlates associated with ADHD.
    - Need to establish that APAP induced liver toxicity in pregnant rats would not confound findings in offspring.
- Potential testing strategies:
    - Conduct standard design rat PPND study with APAP and include cognitive and motor endpoints.
    - Examine APAP/APAP metabolite neuronal toxicity in vitro in primary human neuronal cell culture.
    - Objective should be to design hypothesis-driven experiments and avoid going on a ‘fishing expedition.’
- Who would conduct such studies?
    - NCTR?
    - NTP?
- Additional considerations: Important to avoid over-stating risks associated with APAP.
- Also important to convey risks of APAP in the context of risks of taking alternative pain medications during pregnancy.

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Current Status

A follow-up meeting of the TSI-1355 team was held on 15 November 2017. The nonclinical teams from DNDP and DAAAP presented options for nonclinical testing, in addition to concerns raised by the NAS. A decision was made to take this issue before the OND Medical Policy Team. This meeting is currently scheduled for 24 January 2018.

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Appendix 1

TSI-1355: Maternal APAP Exposure in Pregnancy & Potential Neurobehavioral Effects in Offspring

- Nonclinical Pharmacology/Toxicology Literature Evaluation

Reference	Type of study	Species: strain	Acetaminophen Dose	Age at dosing	Age at testing	Author's conclusion
Blecharz-Klin, 2016	PPND	Rats: Wistar	0, 5 or 15 mg/kg/day in DW	GD-1 to PND-60	PND-60	Slight changes in cerebellar concentrations of monoamines, metabolites, and AAs observed.
Dean, 2016	Fertility/EFD	Rats: Wistar	350 mg/kg PO; GD-13.5 to GD-21.5	In utero	Fetal, PND-25; PND-90	The effects of APAP dosing to pregnant rats on germ cell development and reproductive function in F1and F2 generations were assessed. The authors conclude that in utero APAP exposure alters fetal germ cell number and development in both male and female fetuses.
Fukushima, 2017	Acute (SD)	Mice: ddY (male)	300 mg/kg IP	5-6 Weeks	5-6 Weeks	The role of the serotonergic system in the hypothermic effects of APAP were assessed in the presence of PCPA (serotonin synthesis inhibitor), fluoxetine

						(serotonin reuptake inhibitor), and cyproheptadine ($5HT_2$ antagonist). Authors conclude that serotonergic system does not mediate APAP hypothermic effects.
Mallet, 2008	Acute (SD)	Rats: SD (male) Mice: CD1 (male)	100-600 mg/kg PO 1-10 mg/kg IP	~6-7 Weeks	~6-7 Weeks	The role of the endocannabinoid system in mediating the analgesic effects of APAP was assessed. Authors conclude that FAAH-dependent metabolism of APAP into AM404 results in indirect effects on serotonergic pathways via CB_1 receptors.
Muramatsu, 2016	Acute (SD)	Rats: Crl:CD(SD)	20 mg/kg	PND-42	PND-42	Plasma and brain APAP and AM404 PK were assessed and suggest similar profiles.
Philippot, 2017	Juvenile animal	Mice: NMRI	30 mg/kg, 60 mg/kg (30 mg/kg x 2)	PND 3, 10, 19	2 months	Increased locomotion/ rearing/total activity in animals dosed at PND 3, 10
Saad, 2016	EFD	Mice: CD1	0 (0.5% CMC) or 150 mg/kg/day PO; GD-7 to GD-21	In utero	PND-30	--Maternal serum APAP C_{max} = 117 µg/mL

						--Maternal serum ALT not different from control --No differences in vertical, horizontal, or total locomotor activity at PND-30 (APAP vs. control) --No differences in MRI volume of 29 brain regions or neuronal density at PND-30.
Viberg, 2014	Juvenile animal	Mice: NMRI	60 mg/kg (30 mg/kg x 2)	PND 10	2 months	--Increased locomotion/rearing / total activity in animals dosed at 60 mg/kg at 40-60 min post-dose. --Increased numbers of errors/total time in a radial arm maze post-dose at 60 mg/kg. --Latency of response to hot plate performance? (Hard to interpret considering overlapping SD). --Performance in elevated maze? (Hard to interpret considering overlapping SD).
Wu, 2016	EFD	Mice: KM	0 (PBS) or 300 mg/kg/day PO; GD-13 and GD-14	In utero	PND-21	Impaired glucose tolerance, reduced insulin concentration and

						hepatic glycogen content, and reduced GLUT2 expression in APAP-exposed offspring.
Zaitone, 2012	Juvenile animal	Mice: BALB/c	25, 50, 100, 200 mg/kg	3-4 months	3-4 months	Increased open-arm time/open-arm entries/total head dips at 100 and 200 mg/kg

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/s/

DONALD C THOMPSON
12/04/2017

JANE J SOHN
12/04/2017
I concur.